December 5, 2025

Marty Makary, MD, MPH
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

RE: FDA 483 Observation to AATB Member Establishment Regarding Sepsis—Request for Meeting to Discuss Approach to Sepsis in Donor Eligibility Decisions

Dear Commissioner Makary:

The Association for Advancing Tissue and Biologics (AATB) is a non-profit organization dedicated to advancing the safety, quality, availability and benefits of donated human tissue for transplantation worldwide. AATB achieves this through standards development, accreditation, education, and collaboration with regulatory partners to ensure donated tissue has the greatest impact on patient care.

We write to express urgent concerns over a significant shift in the FDA's approach to sepsis in donor eligibility, evidenced by a recent FDA 483 observation issued to an accredited AATB member. We request a meeting to present our concerns in more detail and discuss evidence-based policy solutions to prevent infectious disease transmission.

Background: Historical Approach to Sepsis in Donor Eligibility

Historically, the FDA's 2007 HCT/P Donor Eligibility Guidance[1] has allowed medical directors to conduct a comprehensive, case-by-case evaluation to determine if a donor with a sepsis diagnosis posed a transmissible infection risk. This process empowered medical directors to use their clinical judgment and all available data to assess true risk, rather than relying on a sepsis diagnosis alone.

This risk-based system has protected recipients for nearly two decades with a strong safety record. Following two rare but tragic *Mycobacterium tuberculosis* (MTB) transmission events in 2021 and 2023, the tissue community's commitment to safety was demonstrated through action by AATB to further strengthen donor screening in the AATB *Standards for Tissue Banking*, 15th Edition (Standards).[2] As discussed below, AATB convened experts to develop and implement new, evidence-based standards to mitigate MTB transmission risk.

[1] FDA Guidance, "Eligibility Determinations for Donors of Human Cells, Tissues, and Cellular and Tissue -Based Products (HCT/Ps)" (August 2007), available at https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Eligibility-Determination-for-Donors-of-Human-Cells--Tissues--and-Cellular-and-Tissue-Based-Products--Guidance-for-Industry.pdf.
[2] See AATB announcements of 2022 recommendations and 2024 revision of *Standards for Tissue Banking*, 15th ed.

Recent FDA Actions: A Shift Toward Rigid Exclusion

AATB shares FDA's goal of preventing any occurrence of an infectious disease transmission associated with tissue transplantation. At the same time, we are concerned that the agency's new approach is an overcorrection that may have unintended negative consequences for patients. The aforementioned FDA 483 observation issued recently to our member treats any sepsis diagnosis as an automatic disqualifier unless a treating physician has documented its resolution. This new interpretation departs from established practice and mirrors the rigid framework described in FDA's draft guidance, issued in May 2025, which AATB and others have cautioned against adopting.[3]

Concerns with the New Interpretation

1. **Medical Directors Are Best Situated to Evaluate Risk at the Time of a Patient's Death**
   FDA's new application of donor eligibility requirements would require tissue establishment medical directors to determine that a potential donor is ineligible if their medical records document sepsis without a subsequent documentation of resolution of sepsis. By treating any sepsis diagnosis as a bright-line exclusion, the FDA's expectation appears to have shifted from a nuanced, evidence-based process to a formulaic approach that does not account for the complexity of clinical practice or the realities of modern medical record documentation. The tissue establishment medical director typically has more comprehensive data available to assess the potential for a systemic infection than the treating physician, which is a better indicator of potentially transmissible disease. It is unlikely that a treating physician will perform a retrospective review and update a donor's medical records several months after the patient has died; so a tissue establishment medical director is better positioned to review whether the donor tissue is safe to accept for transplantation.

2. **Concerns with 2025 Draft Sepsis Guidance**
   AATB believes FDA's actions represent a change in application of the 2007 donor eligibility guidance, not premature implementation of the unfinalized 2025 draft sepsis guidance, but we note that many of our concerns regarding this new application of the 2007 guidance accentuate our concerns with the 2025 draft guidance. We encourage the Agency to work with AATB to minimize any unintended consequences that would arise from finalizing the 2025 draft guidance.

3. **Sepsis as a Surrogate for Transmissible Systemic Infection Is Flawed**
   Current guidelines acknowledge that sepsis syndrome is *typically* triggered by an infection, but there is not always an infection present. The syndrome can be triggered by other conditions, or even an infection that is not systemic or even difficult to treat – such as a urinary tract infection.[4] The actual risk to tissue recipients arises from transmissible systemic infections, not from the sepsis syndrome per se. Therefore, using a sepsis diagnosis as a surrogate for

[3] FDA Draft Guidance, "Recommendations to Reduce the Risk of Transmission of Disease Agents Associated with Sepsis by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (May 2025), available at https://www.fda.gov/media/186261/download (hereinafter "2025 draft guidance").

[4] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

transmissible infection is overinclusive and may lead to unnecessary exclusion of safe donors. Further, since MTB rarely causes clinical sepsis, this approach unnecessarily excludes safe donors and reduces tissue availability without a corresponding safety benefit.[5,6,7,8]

4. **Impact on Donor Availability and Patient Access**
   Rigid exclusion based on a prior sepsis diagnosis could reduce donor availability by about 25 percent, as shown by the attached AATB pilot study, which found that 23 percent of deceased donors had a sepsis diagnosis; the study also showed that 38 percent had either a sepsis diagnosis or met Systemic Inflammatory Response Syndrome (SIRS) criteria, meaning donor availability could be reduced by more than one-third if both a sepsis diagnosis or meeting SIRS criteria require donors to be excluded. Such a reduction could have a devastating impact on tissue availability without a corresponding increase in safety.

Evidence-Based Recommendations for Donor Screening

AATB shares the FDA's goal of preventing tissue-transmissible infections. We think it is also important to preserve patient access to safe, life-enhancing tissue. Instead of disqualifying all donors with a sepsis diagnosis in the medical records, we continue to advocate an approach that:

- Empowers medical directors to use their clinical judgment and all available data to assess the true risk of transmissible infection. The AATB Standards have always prioritized a screening approach in which tissue bank medical directors evaluate the potential for a transmissible infection based on a range of objective evidence of systemic infection—such as laboratory, microbiological, and imaging results—rather than rely solely on the presence of a sepsis diagnosis in the medical record. This approach is more closely aligned with the actual risk of transmissible infection and is supported by the tissue banking community and infectious disease experts.

- Recognizes the limitations of medical records, including the infrequent documentation of sepsis resolution by the treating physician, and the frequency with which a sepsis diagnosis is made but represents *suspected* but not *confirmed* infection based on the patient's observed symptoms.[9,10] Medical records frequently contain outdated or redundant diagnoses due to copy--paste (or "copy-forward") errors and lack of active documentation, making the presence

[5] Arya V, Shukla AK, Prakash B, et al. Tuberculosis-Associated Septic Shock: A Case Series. *Cureus*. 2022;14(3):e23259. Published 2022 Mar 17. doi:10.7759/cureus.23259

[6] Mishra R, Patel HK, Singasani R, Vakde T. Tuberculosis septic shock, an elusive pathophysiology and hurdles in management: A case report and review of literature. *World J Crit Care Med*. 2019;8(5):72-81. Published 2019 Sep 11. doi:10.5492/wjccm.v8.i5.72

[7] Tang Y, Zhu Y, You Z. Mycobacterium tuberculosis sepsis with multiple intermuscular abscesses and respiratory failure as the main manifestations: a case report. *BMC Infect Dis*. 2024;24(1):340. Published 2024 Mar 21. doi:10.1186/s12879-024-09187-2

[8] Bridges DA, Bedimo RG. Severe Tuberculosis Sepsis in an Immunocompetent Patient. *Am J Med*. 2006;119(3):e11-e14. doi:10.1016/j.amjmed.2005.08.033

[9] Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis. JAMA. 2016;315(8):762. doi:10.1001/jama.2016.0288

[10] Rhee C, Jones TM, Hamad Y, et al. Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals. JAMA Netw Open. 2019;2(2):e187571. doi:10.1001/jamanetworkopen.2018.7571

of a sepsis diagnosis an unreliable indicator of current infection risk. Furthermore, documentation of sepsis resolution or rule-out is infrequent, so requiring such documentation as a condition for eligibility is neither evidence-based nor practical.

To meet these goals, while still improving screening practices, last year we adopted new requirements in the *Standards* to more comprehensively evaluate donors for risk of MTB in tissue donor screening, with implementation required by January 31, 2025. These new requirements were developed in direct response to recent MTB transmission events linked to viable bone allograft products and were informed by a multidisciplinary working group, including infectious disease experts, using information from federal agencies and other sources. The new requirements are designed to provide robust, evidence-based criteria for donor screening and evaluation and prevent disease transmission in all tissue donors, not only those donors diagnosed with sepsis.

Key elements of the new requirements are the stratification of risk for MTB based on tissue processing methods—distinguishing between highly processed tissues and those that are minimally processed or contain viable cells—and requirements for enhanced donor screening based on exposure and reactivation risk factors. This approach incorporates epidemiologic and clinical data to better assess donor risk for MTB and in doing so it provides stringent exclusionary criteria for MTB. The approach also supports a nuanced, risk-based eligibility determination for sepsis that better reflects the true risk of transmissible infection. The end result is a framework that results in the exclusion of all donors with risk factors for, and clinical evidence of, relevant communicable disease agents and diseases (RCDADs), consistent with our belief that minimally processed tissue, and tissue containing viable cells, should be subject to more stringent requirements than those that will be highly processed. Ultimately, this combined approach to MTB and sepsis screening is evidence-based and stratifies risk to enhance both the safety and availability of donated tissue, and ensures that exclusion decisions are grounded in the best available science and clinical practice, rather than rigid reliance on syndromic labels or incomplete documentation.

There's more to come: AATB is developing evidence-based guidelines to help medical directors make well-informed decisions about systemic infection risk. The guidelines will define what data are necessary to make those well-informed decisions (under varying clinical circumstances) and will advise medical directors on documentation of the reasons for those decisions. These guidelines will consider risk associated with a donor's medical history, circumstances of death, and the planned tissue processing approach. We also plan to build on the AATB pilot study with a new study performed by the Chronic Disease Research Group of the Hennepin Health Research Institute that will examine the process of ruling out potential tissue donors, and we will include a focus on sepsis or suspicion of sepsis in the analysis.

We are also aware that the Office of the Inspector General (OIG) is expected to release a report in 2026 examining how hospitals in the United States are defining sepsis. Many professional societies, clinical groups, and the OIG have noted that hospital coding and billing practices around sepsis can vary as a

function of billing incentives and are rife with accuracy concerns.[11,12] While these efforts by AATB and OIG are currently incomplete, we believe the AATB pilot study demonstrated that a sepsis diagnosis alone is not a reliable predictor of MTB or other transmissible infections. Medical directors can effectively evaluate risk using a more nuanced, evidence-based approach.

Conclusion

In sum, our position is grounded in scientific evidence demonstrating that sepsis is a clinical syndrome that is not necessarily indicative of a systemic or transmissible infection. The enhanced AATB Standards are designed to exclude all donors with major MTB risk factors from donating tissues, and to require additional donor exclusions for donors of the riskiest tissue. These new donor screening requirements address the MTB risks directly, rather than relying on the non-sensitive and non-specific sepsis diagnosis as a surrogate for MTB or other infections. AATB and its Physicians Council will soon publish new guidelines and *Standards* requirements regarding the evaluation of donors with a risk of systemic infection. This approach will still empower medical directors to use objective clinical data and their professional judgment, addressing the well-documented limitations of medical record documentation, without compromising safety. The alternative approach of rigid exclusion based on a sepsis diagnosis in the medical records, without medical director judgment, could unnecessarily reduce the supply of life-saving tissue for transplant by about 25 percent, without significantly improving safety.

Given the public health implications of this policy shift, we request a meeting in January 2026 to discuss our concerns and evidence-based solutions to prevent infectious disease transmission. We urge the FDA to reconsider its approach and not reject the foundational framework that has provided an exceptional level of safety for nearly two decades.

Thank you for your attention to this critical issue. We look forward to discussing our concerns and collaborating with the FDA on policies that ensure the safety and availability of donated human tissue.

Respectfully,

Marc Pearce
President & CEO
Association for Advancing Tissue and Biologics

CC: Vinay Prasad, MD, MPH, Chief Medical and Scientific Officer – Office of the Commissioner, Director – Center for Biologics Evaluation and Research

[11] Sand J, Kuqi A. Current Challenges in Sepsis Documentation and Coding: A Review of the Literature. Coding. 2023;20(3). Accessed June 9, 2025. https://ahisp.ahima.org/page/currentchallenges-in-sepsis-documentation-and-coding-a-review-of-the-literature

[12] US Department of Health and Human Services Office of Inspector General. Medicare Inpatient Hospital Billing for Sepsis. US Department of Health and Human Services Website. March 2024. Accessed June 9, 2025. https://oig.hhs.gov/reports-andpublications/workplan/summary/wp-summary-0000841.asp

Attachments:

A. AATB Pilot Study Report on Sepsis Criteria

B. AATB Sepsis Comments

Pilot Study Report on Sepsis Criteria

About This Report

This December 2025 report was developed by the AATB Physician Council Sepsis Working Group and originally made available in September 2024. Since then, additional review and analysis of the data and methodology have been provided by Jonathan M. Miller and Maria Masotti, of the Hennepin Healthcare Research Institute, along with minor edits and revisions that are intended to provide additional context since the original release of the report.

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Background

According to FDA regulations, tissue establishments recovering and processing tissues for the purpose of transplantation are required to have "appropriate screening measures that have been developed for detection of sepsis, such as the medical history interview, and clinical and physical evidence." In accordance with 21 CFR § 1271.75: "Persons who are deceased and have a documented medical diagnosis of sepsis or have documented clinical evidence consistent with a diagnosis of sepsis that is not explained by other clinical conditions at the time of death" should be excluded. The guidance also advises that deceased donors may still be eligible if they had an initial diagnosis of sepsis which has been ruled out.[1]

Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" with life threating physiologic derangement.[2] A diagnosis of sepsis in the hospital and emergency room setting has become exceedingly common in the United States and worldwide in the past decade, most likely due at least in part to the Surviving Sepsis Campaign (SSC). SSC is a global initiative to develop and increase awareness of the scope of sepsis syndrome. The goal of this campaign has been to provide successful quality improvement techniques through published guidelines for the treatment of sepsis in addition to guideline implementation, behavior change, and data collection. The SSC has significantly influenced the screening and management of sepsis in the United States and worldwide, with ongoing revisions and updates most recently in the Sepsis 3 recommendations.[2] The sepsis syndrome can be promptly identified at the bedside with quick Sepsis-related Organ Failure Assessment (qSOFA), which includes two of the following three components: an alteration in mental status, systolic blood pressure ≤ 100 mm Hg, or respiratory rate ≥22/min.[2] With these tools for early recognition of sepsis and ease of diagnosis, the syndrome is currently estimated to be among the top single most common diagnoses in US hospitals.[3–7] Other causes for the increased reported incidence of sepsis could include aging populations with more comorbidities and the use of reimbursement-favorable coding.[8–11]

In correspondence to FDA on July 7, 2025, AATB noted the challenges associated with accurately diagnosing a condition that may be harmful to tissue recipients: "[t]he fact that there are different definitions of sepsis in use today is a challenge that is exacerbated by two important changes that have occurred in US healthcare since sepsis was first considered an RCDAD in 2007, both of which contribute to an increase in the likelihood that clinical impressions or working diagnoses are labeled as sepsis. These changes

include a number of payment reforms instituted by the Centers for Medicare and Medicaid Services (CMS), as well as the increase in adoption of electronic medical records."

The letter also notes that "[m]any professional societies, clinical groups, and even the Office of the Inspector General (OIG) have noted that hospital coding and billing practices around sepsis can vary as a function of billing incentives and are rife with accuracy concerns (OIG is expected to release a report in 2026 determining if hospitals in the US are relying on a broader definition of sepsis that is favored by CDC and CMS)." [10,11]

The letter goes on to add that "[c]linicians often include sepsis in a differential diagnosis to ensure timely and potentially life-saving treatment. However, subsequent diagnostic evaluation frequently reveals that the physiological manifestations initially attributed to sepsis may instead be due to non-infectious etiologies. As such, the presence of a sepsis diagnosis alone may not reliably indicate an underlying transmissible infectious disease."

The use of electronic medical records presents an additional challenge. While electronic medical records (EMR) have greatly streamlined the various aspects of health care flow and reduced some time-consuming aspects of documentation and charting, they have also produced exceedingly long, occasionally inaccurate notes with redundancy, inconsistency, and outdated information. The use of copy and paste and copy forward functions used by an overwhelming number of clinicians/health care workers can inadvertently result in the passive repetition of patient problem lists, even when some of the patient problems may have been completely resolved. Active documentation is required to remove or update a patient problem in the EMR. This documentation is often completely skipped, resulting in long problem and discharge diagnoses lists which are not updated.[12]

To avoid unnecessary donor exclusions, tissue banks who recognized these redundant issues with EMR documentation have developed various strategies to comb through the records in order to screen donors who may be eligible to donate because of evidence of resolution of sepsis or evidence that sepsis was ruled out. Many of the tissue banks have multiple medical reviewer policies and regular medical director meetings to discuss complex donor cases.

Recently, viable tissue products were produced from two donors who were later found to have tuberculosis. There were significant morbidity and mortality caused by outbreaks of tuberculosis after using these viable cell products. Understandably, both the AATB and FDA were very concerned after these events. It is predicted that in the aftermath, the FDA will

further restrict acceptance of donors who may not have had systemic transmissible infection at time of death by further tightening the sepsis criteria. It is the hope of this AATB Physicians Council Sepsis Working Group, along with several major volunteering tissue banks, that this prospective chart review study would quantify the number of donors who had sepsis documented in their charts, the number of donors considered to be truly septic, and finally, the number of donors who would be excluded if FDA requires more stringent criteria for sepsis-related donor eligibility.

Frequency of sepsis diagnosis among individuals with in-hospital deaths

Sepsis is a growing worldwide healthcare challenge associated with significant morbidity and mortality. In 2017 there were an estimated 49 million cases of sepsis recorded worldwide with 11 million sepsis-related deaths. This accounted for 19.7% of all global deaths.[13] In 2018, sepsis/septicemia was the most common non-maternal/neonatal primary diagnosis in the United States accounting for 2,218,755 or 8% of all hospital admissions.8 The number of sepsis admissions increased to 2,446,047 by 2021.[14]

Sepsis is not only the most common primary diagnosis among hospitalizations but also a common secondary diagnosis. The number of hospital discharges associated with a diagnosis of sepsis noted during the admission has steadily increased from 2.74 million to 3.2 million from 2017-2021.8 (Fig. 1) Although the rate of in-hospital deaths related to sepsis had been declining prior to 2019, sepsis related deaths spiked to 12.5% in 2021, likely related to the COVID19 pandemic.8 (Fig. 2) Furthermore, sepsis disproportionately impacts older patients. The diagnosis of sepsis among adults aged 65 and older has increased by 7% since 2016, accounting for 1.4 million or 56% of all inpatient sepsis-related stays by 2021.[3]

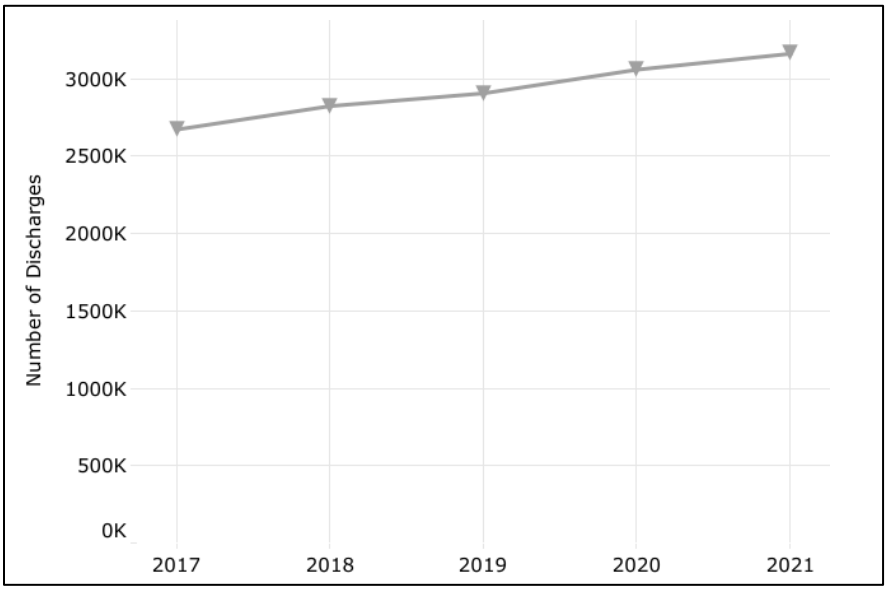

Figure 1. Number of hospital discharges in the U.S. with a listed diagnosis of sepsis/septicemia during admission, 2017-2021.[3]

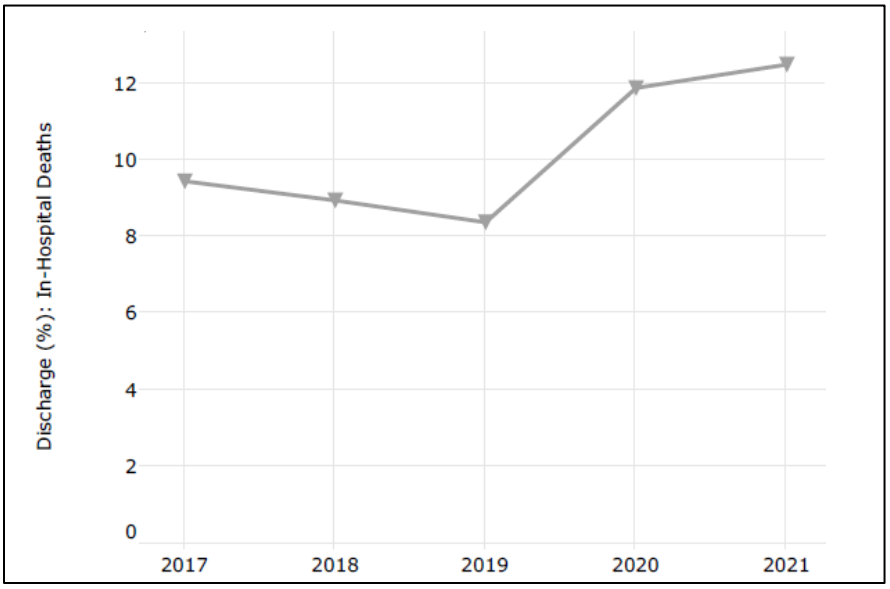

Figure 2. Percentage of U.S. in-hospital deaths with a primary diagnosis of sepsis/septicemia, 2017-2021.[3]

It is important to note that most data reported on sepsis rates include all hospital patients, the majority of whom survived their admission. However, the cohort of potential cadaveric

HCT/P donors is comprised exclusively of individuals who die. Therefore, rates of sepsis among hospital deaths provide data more relevant to tissue donation. A 2014 retrospective analysis using the Sepsis-3 criteria of 2.9 million adult admissions in 409 hospitals showed an overall hospital sepsis incidence of 6% and that sepsis was present in 35% of all hospitalizations culminating in death.[15] Also in 2014, Liu reported on hospital deaths in patients with sepsis from two independent patient cohorts from the Kaiser Permanente Northern California (KPNC) healthcare system (N=482,828 admissions/14,206 deaths) and the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) (N=6.5 million admissions/143,312 deaths). The authors identified patients with either an explicit ICD-9 diagnosis code of sepsis, severe sepsis, septic shock, or septicemia or an implicit diagnosis which included the addition of patients with evidence of both an infection and acute organ failure. The KPNC cohort showed an 11% explicit and 17% implicit overall rate of sepsis. The NIS cohort had an overall 4% explicit and 11% implicit rate of sepsis diagnosis. Among the KPNC deaths, 37% had an explicit diagnosis of sepsis and 56% had an implicit septic diagnosis. The NIS deaths showed a 35% explicit and 52% implicit rate of sepsis diagnosis.[16] A 2018 retrospective cohort study of 568 adults from 6 US hospitals who either died in the hospital or were discharged to hospice showed that sepsis (possible, probable, or definite) was present during hospitalization in 300 (53%) patients and was the immediate cause of death in 198 cases (35%).[17]

In summary, these data indicate that a diagnosis of sepsis impacts approximately 35% of the potential in-hospital cadaveric HCT/P donors. More significantly, when clinical criteria such as infection coupled with organ dysfunction is added, over 50% of potential in-hospital cadaveric donors are impacted.

Pilot Study Methods

Pilot Study Data Collection Methods:

This prospective pilot study aimed to primarily evaluate the incidence of sepsis diagnosis, satisfaction of sepsis diagnostic criteria, and medical director suspicion of true transmissible infection via tissue donor chart review. A structured survey tool was designed to collect the appropriate data, and accompanying instructions were provided. Participants were medical directors from the AATB Sepsis Working Group who volunteered to independently complete the survey tool and included those from several large tissue banks with diverse areas of medical expertise.

Between July 15 and August 8, 2024, medical directors filled out the data collection tool concurrently with donor chart review for every donor record participating medical directors reviewed during that time. Medical directors representing seven tissue establishments participated in this prospective data collection effort. Charts were de-identified to maintain confidentiality.

The data collection tool (Appendix 1) and instructions for the pilot study are provided (Appendix 2).

Data Collected during Pilot:

A. Chart number
B. Chart Review Date
C. Donor ID (de-identified/not provided)
D. Sepsis Diagnosed During Hospital Stay (in problem list or discharge diagnosis) [corresponds to first part of sepsis screening criteria in current DE guidance]
E. SIRS (or SOFA) + Suspicion of Infection criteria met? [corresponds to second part of sepsis screening criteria in current DE guidance]
F. If yes, was sepsis later "ruled out" by treating MD?
G. Sepsis is not diagnosed in the chart, but medical director believes there is potential for transmissible infection
H. Transmissible/ suspected infection treated appropriately and not a concern at TOD
I. Medical director believes true risk of transmissible infection present?
J. Cause of Death?
K. Notes

Experiences with using the data collection tool and the results from the pilot data were reviewed as a working group after the pilot completion. The instructions and data collection tool were refined for clarity in preparation for a larger effort (if appropriate), and the date of recovery was added to the data collection tool for future use.

Results

Simple descriptive statistics of the dataset are provided. Diagnostic agreement between different proposed criteria with the medical directors' assessments were estimated by sensitivity, specificity, positive predictive value, and negative predictive value. Raw data are available. (Appendix 3)

Total number of donor charts reviewed was 486 (n=486).

Total Number of charts with Sepsis diagnosis were 112, as a percentage of the total number of charts reviewed (112/486) 23.0%.

Six charts had diagnosis of sepsis but did not meet SIRS criteria.

Total Number of charts with Sepsis that ALSO met SIRS Criteria were 106, showing that 95% of donors diagnosed with sepsis (112) also met SIRS criteria (106/112=95%) and as percentage of total chart reviewed were 21.8%. SIRS criteria were not assessed in 58 cases (11.9%), none of which had a diagnosis of sepsis.

Total number of charts meeting SIRS criteria + suspicion of infection but NOT diagnosed with Sepsis were 73, or 15 % of the total number of charts reviewed (73/486).

Total number of charts with sepsis diagnosed where sepsis was later "ruled out" by the treating provider and documented in the medical records were 13.

Total Number of Donors diagnosed with Sepsis for which the Medical Director believes the suspected infection was treated appropriately and therefore is not a concern at the time of death were 64 donors.

- As a percentage of charts with diagnosis of Sepsis (64/112) = 57%
- As a percentage of donor charts meeting Sepsis + SIRS (64/106) = 60%
- As a percentage of all donor charts reviewed (64/486) = 13%

The total Number of Donors for which the Medical Director believed a true risk of transmissible infection is present was 30 or 6.2% of the total number of charts reviewed (30/486). Risk of transmissible infection was missing for 5 (1%) of the charts, none of which had a sepsis diagnosis or met SIRS criteria.

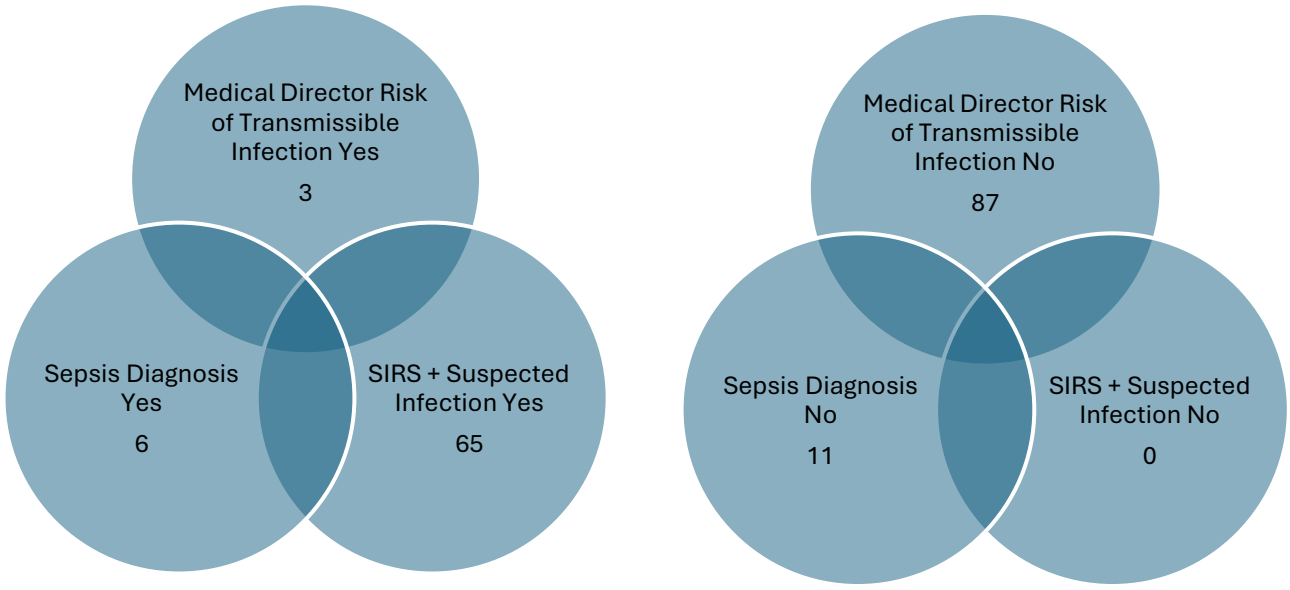

Figure 3: Donor Charts Venn Diagram of Rule-outs (left) and Rule-ins (Right)

We enumerated the total Number of Donors for which the Medical Director believed there is a true risk of transmissible infection present

- As a percentage of the total charts meeting Sepsis Diagnosed AND met SIRS Criteria AND had suspicion of infection, 17.9% (19/106 charts).
- As a percentage of charts meeting SIRS + suspicion of infection only with no sepsis diagnosis in chart, 11.0% (8/73 charts).
- As a percentage of charts with sepsis later documented as ruled out by the provider, 5.0% (2/40 charts).
- As a percentage of charts with donors deemed to have their suspected infection treated appropriately, 3.8% (3/78 charts)

We assessed the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each criterion based on the medical director's assessment of true risk of transmissible infection (Table 1).

- Only 63% of the donors ruled high-risk for transmissible infection by the medical director would be ruled out by a sepsis diagnosis alone, while 21% of the donors ruled in for donation by the medical director would be ruled out based on a sepsis diagnosis. The probability that a donor with a sepsis diagnosis will be deemed high risk by the medical director is only 17%. The probability that a donor without a sepsis diagnosis will be deemed high risk by the medical director is 3%.

- 96% of the donors ruled high-risk for transmissible infection by the medical director would be ruled out by a criterion based on SIRS + suspected infection, while 38% of the donors ruled in for donation by the medical director would be ruled out based on SIRS + suspected infection. The probability that a donor with SIRS + suspicion of sepsis will be deemed high risk by the medical director is only 15%. The probability that a donor without SIRS + suspicion of sepsis will be deemed high risk by the medical director is .4%.
- Only 68% of the donors ruled high-risk for transmissible infection by the medical director would be ruled out by a sepsis diagnosis AND SIRS + suspected infection, while 22% of the donors ruled in for donation by the medical director would be ruled out based on a sepsis diagnosis AND SIRS + suspected infection. The probability that a donor with sepsis diagnosis and SIRS + suspicion of sepsis will be deemed high risk by the medical director is only 18%. The probability that a donor without diagnosis or SIRS + suspicion of sepsis will be deemed high risk by the medical director is 3%.
- 90% of the donors ruled high-risk for transmissible infection by the medical director would be ruled out by a criterion based on sepsis diagnosis OR SIRS + suspected infection, while 35% of the donors ruled in for donation by the medical director would be ruled out based on sepsis diagnosis OR SIRS + suspected infection. The probability that a donor with sepsis diagnosis or SIRS/SOFA + suspicion of sepsis will be deemed high risk by the medical director is only 15%. The probability that a donor without sepsis diagnosis and SIRS/SOFA + suspicion of sepsis will be deemed high risk by the medical director is 1%.

Table 1. Rule-out Accuracy of Criteria based on Medical Director's Assessment of True Risk of Transmissible Infection

Criterion	Sensitivity	Specificity	PPV	NPV
Sepsis Diagnosis	63.3%	79.4%	17.0%	97.0%
SIRS + Suspected infection	96.4%	61.6%	15.1%	99.6%
Sepsis Diagnosis AND SIRS + Suspected infection	67.9%	78.0%	17.9%	97.2%
Sepsis Diagnosis OR SIRS + Suspected infection	90.0%	65.0%	14.6%	99.0%

Discussion

Our data indicates that a sepsis diagnosis is present in 23% of donor charts reviewed, whereas a diagnosis of sepsis that also meets SIRS criteria plus suspicion of infection was found in 22% of donor charts. When a sepsis diagnosis is present in the donor chart, there is a high likelihood that donor will also have met SIRS criteria. In fact, the combination of criteria had similar sensitivity as sepsis diagnosis alone in assessing the medical director's assessment of the risk of transmissible infection. The study did not evaluate those donors who were excluded by pre-screeners due to infection/sepsis concerns, due to those charts never making it to review by medical directors, suggesting that the percentage of sepsis diagnosis in overall deceased donors is at least larger than 23%. Literature review indicated that a diagnosis of sepsis impacts approximately 35% (at least one third of donors) of the potential in-hospital cadaveric HCT/P donor pool (see details above).

The study shows that among Tissue Bank Medical Directors evaluating donor charts for potential of transmissible infections, the diagnosis of sepsis is considered concerning for transmissible infectious risk in only 17.9% of charts meeting both "Sepsis Diagnosed" AND "SIRS Criteria + suspicion of infection" (19/106). The proportion of donors with sepsis diagnosis AND SIRS + suspicion of sepsis that are deemed low risk by the medical director is a substantial 82.1%. This conclusion is usually reached because infection transmissibility by tissue is evaluated by taking into consideration multiple aspects of the donor and the tissue intended for transplant and not solely based on finding sepsis documentation in the chart. Sepsis, being neither specific nor diagnostic of transmissible infections by tissues, is taken into consideration as one item among many and is not the sole determinant of eligibility. Other factors evaluated include the medical, social and behavioral history of the donor which determines epidemiologic exposures, immune status, susceptibility to infections and potential of harboring certain transmissible infections. The physical exam findings, laboratory, microbiological and imaging data are also evaluated. Occasionally donors may also have autopsy, biopsies with histologic exams, or known outcomes of organ transplant, further contributing to the risk assessment process.

Sepsis is a crucial diagnosis to be made early in course of admission to improve outcomes in patients with significant physiological derangements and hence clinicians tend to document and act on it, regardless of whether there is any evidence of infection or if there

is another clear diagnosis that explains the physiological derangements. Even with abundant evidence of absence of infection, documentation of "sepsis resolved" or "sepsis ruled out" is infrequent; our study showed such documentation was made in only about 12% (13/112) of charts with a sepsis diagnosis. This is due to several reasons, some of which were highlighted in the background section above. Our data collection notes section (see Appendix 1, Column J) shows cause of death of the donors with sepsis documentation, other than infection, included conditions like myocardial infarction, stroke, COPD, metabolic, brain anoxia due to drug overdose, and trauma which can produce physiologic derangements that meet criteria of systemic inflammation plus or minus organ dysfunction, which is used to make a diagnosis of sepsis at the bedside. It is understood that "culture/ work up negative infectious work up" may not exclude certain infections with organisms that are difficult to detect, such as mycobacteria, mycoplasma, certain viruses and fungi. However it is also understood that these types of infections are not the most common causes of sepsis in US hospitals and moreover more frequently infect certain populations with certain risk factors, already being screened for by other parts of donor screening such as, IVDU and other high risk behavior, alcohol use disorder, homelessness, travel and other exposures and epidemiologic factors, medical history that assesses donor immune function, and hence vulnerability to certain difficult-to-detect organisms.[18,19]

The pilot study shows that the total percentage of donors who had either a sepsis diagnosis or met SIRS criteria constituted about 38% of charts reviewed. About 35% of low-risk donors as assessed by the medical director would be ruled-out using diagnosis OR SIRS + suspected infection as the criterion. On the other hand, using diagnosis AND SIRS + suspected infection would only result in 22% of donors, deemed low risk by the medical director being ruled out.

Data Strengths:

- This prospective study collected real-time data from seven large tissue establishments by experienced medical directors who are very familiar with reviewing medical records of deceased donors.
- A large number of charts were reviewed to produce the data set (486).
- Data collection criteria provided a mix of objective and subjective data collection, same as the real-life process of donor eligibility determination.
- The data collected includes data from multiple medical directors and multiple processors.

Data Limitations:

- Convenience sample of donor charts reviewed by medical director members of the Sepsis Working Group over the given period of time:
    - Unable to design a statistically representative sample without knowledge of the total number of donor charts reviewed each year (i.e., no available denominator data)
    - Geographic location of donors is not evaluated/considered
    - The participating tissue establishments represent some of the larger US processors, but this is not considered a representative sample of the types of processors seen across the tissue banking industry, e.g., mid- to small-size establishments are not well-represented
- The donor charts reviewed by medical directors are not representative of all potential donors evaluated by tissue establishments
    - Each establishment has different pre-screening criteria for what donor charts are provided to the medical director for review
    - While the pre-screening criteria varies amongst tissue establishments, no establishment provides all potential donors for medical director review – there is some culling of charts so that some clearly ineligible donors are not included for medical director review
    - While we cannot estimate the extent, the percentage of donor charts with sepsis included as a consideration (either diagnosed with sepsis, or meets suspicion of infection + SIRS/SOFA) in this data set is almost certainly an under-estimate
- There may be variation by season, given the seasonality of many infections:
    - This would be anticipated to be mitigated somewhat by the fact that donor charts are reviewed at varying timeframes after tissue collection (e.g., range of weeks to about a year
    - If more data are collected, we would include the recovery date in the data set
- During the pilot review, we noted some inconsistencies in the interpretation of how to report for Column E. The instructions (see Appendix 2) were as follows:
    - " SIRS (or SOFA) + Suspicion of Infection criteria met? - (Drop down Yes, No, N/A) The SIRS or SOFA criteria PLUS any suspicion of infection."
    - "For purposes of this data collection, we will use the Sepsis-2 and/or Sepsis-3 definitions, which essentially are either SIRS or SOFA (or qSOFA) criteria being met PLUS any suspected infection. If SIRS alone and no

documentation in record of diagnosis or suspicion of infection or sepsis, please do not mark YES"

- Yet, in review the column E header was noted to have been interpreted in various ways. Some marked "Yes" if SIRS alone was met, some only marked "Yes" if SIRS+ suspicion of Infection met, and some marked N/A if Sepsis was not diagnosed in column D. Thus, we are unable to determine with high certainty the true incidence of charts that met SIRS alone without Sepsis diagnosis, vs SIRS+ some suspicion of infection with or without Sepsis diagnosis. If further data were to be collected, Column E would be modified for clarity.
- The number of donors marked as positive for SIRS AND sepsis diagnosis is likely an underestimate of those that would be ineligible if the criteria were Sepsis Dx + SIRS criteria alone (without suspicion of infection explicitly noted), given that Column E in the data collection tool was not consistently interpreted to mean “SIRS Criteria Alone” met, but was designed to include SIRS + suspicion of infection or sepsis (see data limitations below).
- Had Column E solely asked, “Were SIRS criteria met?”, we predict the number marked “Yes” would have been much higher.

- Another limitation to be noted is that the participants of the study are mostly from larger-sized processors who are known to have more selective criteria for what potential donors they would consider reviewing. In other words, it is highly unlikely that the mix of available donor charts amongst non-participants of this pilot study would have a lower sepsis diagnosis rate; in fact, it is the consensus of this working group is that the percentage is likely to be much higher than 23% shown in this study.

Conclusions

- The AATB Physicians Council Sepsis Working Group (PC Sepsis WG) believes the donor screening criteria for “sepsis” would best be aligned with the presence of a true systemic infection transmissible by tissues given that is what produces the actual risk to recipients, not the physiologic response to an infection (i.e., with sepsis being a dysregulated physiological response to a suspected infection, which is in itself is not transmissible). The diagnosis of sepsis is a clinical tool used to prevent morbidity and mortality from an inflammatory response in living patients and is not an accurate predictor of transmissible infection involving transplantable tissue from deceased donors.

- Furthermore, there needs to be greater focus on objective data points such as blood cultures and processing cultures.
- Currently, the donor eligibility guidance permits medical directors to accept donors meeting SIRS/ SOFA criteria if they believe the symptoms are explained by an alternative diagnosis.
    - Sepsis criteria changes that do not allow the medical director to interpret the available data and clinical course of donors meeting SIRS/ SOFA criteria will likely have a significant impact on tissue availability.
- Currently, medical directors feel comfortable accepting donors where there was a clinical diagnosis of sepsis during the hospital stay when a source of infection was identified that was adequately treated prior to death.
    - Sepsis criteria changes that do not permit accepting donors with a diagnosis of sepsis where the infection was adequately treated will likely have a significant impact on tissue availability.
- Currently, medical directors feel comfortable accepting donors where the clinical record indicates that sepsis is resolved (albeit that does not occur frequently).
    - Sepsis criteria changes that do not permit accepting donors with a diagnosis of sepsis where the clinical records formally indicate "sepsis resolved" prior to death will likely also impact tissue availability.
- Potential donors with a diagnosis of sepsis without a clear cause of the physiological response to a possible infection is the most challenging category to assess, as the lack of finding a causative agent for the sepsis response could represent either a difficult to detect infectious agent (e.g., mycobacteria, mycoplasma, viruses, or certain fungi) or a lack of infectious cause – but there are no available data to reliably discern between these possibilities.
    - In such cases it is imperative to risk stratify all donor aspects including medical, social history, immune status, exposures in addition to all available chart data. It is imperative to also consider the type of tissue to be used, understanding that viable products are considered most at risk to transmit donor-related microbes, and act accordingly.
- The AATB Physicians Council Sepsis WG believes that prevention of tuberculosis transmission is best done from the standpoint of improved epidemiologic and risk factor screening and stratification, which has since been implemented through the updated DRAI and eligibility Standards.[20,21] As tuberculosis lesions can "hide" in tissues without causing Sepsis syndrome,[22–25] a more robust and specific analysis tool was needed and created.

- The AATB PC Sepsis WG is working to formulate criteria for screening for tissue transmissible systemic infections, and plan to then develop algorithm/flow chart to aid in making the donor eligibility determination.
- We can foresee that consideration of having stricter sepsis criteria for donors of tissues containing viable cells than donors of highly processed tissues (like AATB developed for MTB donor screening) (Table 2) could be very helpful in balancing safety and availability.

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Sentinel Tissue-Transmission Events published in MMWR since 1979

Date	Tissue Product	Infection	# Infected	Processing	Refs	CDC editorial notes / discussion points
10/10/1978	cornea	rabies	1	Aseptically processed	[1,2]	"This is the first case of rabies acquired from a tissue transplant of any kind. ... This case highlights concern about the transmission of infectious agents by corneal transplants first raised by the report of transmission of Creutzfeldt-Jakob disease by a corneal transplant (2), and suggests that the criteria for accepting donors should be reevaluated. ... These 2 cases demonstrate how hard it is to diagnose rabies if an animal bite is not noted and the patient presents with an ascending paralysis without the excitement and agitation classically associated with rabies. ... As occurred in connection with a recent rabies case in Pennsylvania, the difficulty persons had in remembering the circumstances of their contact with the patients—a contact that occurred 14-100 days earlier — and the many days the patients were not on isolation precautions, resulted in the recommendation that many persons receive rabies post-exposure treatment."
2/1/1988	bone allograft	HIV	1	"The donor's bone was harvested under sterile conditions and stored at -80 C, and no sterilizing procedures were performed. The bone was used in the recipient's surgery 24 days after procurement."	[3,4]	This sentinel event triggered discussions with FDA, CDC, and AATB to discuss donor screening for HIV (and eventually led to promulgation of 1270 regulations); "As previously recommended by AATB, all living donors of bone should be retested at least 90 days after tissue procurement, and only bone from living donors negative for HIV antibody on this repeat testing should be distributed for transplantation (10). Bone from donors not available for retesting, including cadaveric donors, should be used when bone from retested living donors is not available or is not appropriate for use in the anticipated surgical procedure."
6/1/1988 & 5/1/1989	cornea	Strep Pneumoniae	2	Aseptically processed; "Both grafts had been stored in commercially available	[5]	"Staphylococcus epidermidis and Staphylococcus aureus are the most common infecting organisms for postoperative endophthalmitis after corneal transplant surgeries, followed by gram-negative bacilli and various streptococci (6,7). Streptococcus pneumoniae has been reported as an infrequent cause of infection (8-10)...Gentamicin is the sole antibiotic supplement used in commercial cornea storage medium

				McCarey-Kaufman buffered medium containing gentamicin (100 |xg/mL."		because it has been reported to be more effective than penicillin or cephalothin in reducing the colony counts of S. aureus and gram-negative bacilli in a buffered medium (11). ... Thus, use of gentamicin alone in cornea storage media or as prophylaxis following corneal transplant surgery may not prevent the rare complication of pneumococcal endophthalmitis. ... In the four cases described in this report, contamination of the corneal grafts with S. pneumoniae could have occurred before harvest, at harvest, during storage, or at time of transplantation. However, culture of donor corneoscleral tissue indicated that at least one of the grafts had been contaminated with S. pneumoniae before transplantation."
5/1/1996	Aortic valve	Candida albicans endocarditis	1	aseptically processed using antibiotic cocktail incubation and cryopreservation	[6]	Preprocessing culture positive for C. albicans; used antibiotic cocktail soak (including amphotericin B (antifungal), fluconazole (antifungal), vancomycin, Imipenem, and netilmicin) and did re-culture after processing. "Under a proposal published by FDA for regulation of cellular and tissue-based products, human heart valve allografts would be subject to donor screening and testing, processing, labeling, and registration requirements. Additional measures that could be considered by the tissue banking community include standardization and validation of d disinfection methods and identification of culture results that indicate allografts must be discarded."
4/5/2000	Bone-tendon-bone allograft	Septic arthritis	4	Tissue Bank A (Texas) 2 allografts stated the tissues were irradiated; Tissue Bank B (Florida) 2 allografts were [inadvertently] not irradiated	[7]	TB-A, b-t-b allograft 1 recipient grew Pseudomonas aeruginosa, Staphylococcus aureus, and Enterococcus faecalis; TB-A b-t-b allograft 2 recipient grew P. aeruginosa; TB-B, b-t-b allograft 1 recipient grew Citrobacter werkmanii/youngae and group B beta hemolytic streptococci, TB-B btb allograft 2 recipients grew Klebsiella oxytoca and Hafnia alvei. "The epidemiologic and laboratory investigation related to tissue bank A indicated that the allografts were the source of the infection despite no apparent lapses in tissue processing. Cases related to tissue bank B were linked to allografts from a common donor that were released inadvertently before standard terminal sterilization procedures were conducted." ...Concern about possible sterilization-related complications has resulted in musculoskeletal tissues (e.g., bone-tendon-bone allografts) being processed aseptically but is not necessarily sterile. Although aseptic processing avoids

						contamination of tissue at the tissue bank, it does not eliminate contamination originating from the donor that might be inherent to the graft. ... This report underscores the need for 1) standard practices for screening, disinfecting, sterilizing, or discarding potentially contaminated allografts; 2) mechanisms for certification and oversight of tissue banks and adherence to quality standards; 3) a system for reporting and investigating infections (bacterial, viral, or fungal) potentially transmitted through human tissues; and 4) the development of safe and effective sterilization methods for musculoskeletal tissue."
11/7/2001	Bone allograft	Clostridium sordellii	2	Aseptic – femoral condyle (fresh) and meniscus (frozen)	[8,9]	MMWR report emphasized the need for processing that is effective against spores, in addition to retrieval limits and using validated culture methods to detect clostridium if no sporicidal method of processing performed; CDC also emphasized the need to properly validate culture methods and to be careful to obtain adequate specimen samples to be representative of the tissue; "Sterilization of tissue that does not adversely affect the functioning of tissue when transplanted into patients is the best way to reduce the risk for allograft-associated infections."
6/1/2002	Saphenous vein, tendon, bone-tendon-bone	HCV	5	"All tissues had been treated with surface chemicals or antimicrobials. Bone grafts also underwent gamma irradiation."	[10,11]	"At the time of the donor's death in October 2000, his serum had no detectable antibody to hepatitis C virus (anti-HCV). The ensuing investigation conducted by CDC and DHS confirmed that the donor, although anti-HCV negative, was HCV RNA–positive and the probable source of HCV infection for at least eight organ and tissue recipients."... "Of the 32 tissue recipients, three were known to have been HCV-infected before transplantation, and test results were not available for another two (one bone and one tendon with bone recipient). Among the remaining 27 tissue recipients, five probable cases occurred: in one of two recipients of saphenous vein, in one of three recipients of tendon, and in all three recipients of tendon with bone (including the index patient)." ... "No cases occurred in recipients of skin (n = two) or irradiated bone (n = 16). Of the two cornea recipients, one was infected before transplantation. The other recipient was anti-HCV–negative; however, as of March 27, HCV RNA testing had not been performed."... "All cases occurred in recipients of organs or

						soft tissues; **no infections were found among those who had received skin or irradiated bone**." ... "Tissue processing methods (e.g., gamma irradiation) might affect the likelihood of transmission of HCV and other viruses from infected donors (3,9). In this investigation, no cases occurred in recipients of irradiated bone. Irradiation is not applied routinely to all tissue types because it can impair tissue structural integrity."
2/1/2003	Cornea	Clostridial endophthalmitis	2	Aseptically processed	[12]	"This report describes the first reported cases of clostridial endophthalmitis associated with transplantation of contaminated corneal tissue. … These data indicate that corneal transplantation in the United States has a very low risk for endophthalmitis. Clostridial infections after implantation of contaminated allografts were first reported in 2001 among recipients of musculoskeletal tissues from cadaveric donors (6). In that investigation, clostridia were recovered both from tissue recipients and from the donors of the tissues. Difficulties in detecting bacteria in postprocessing cultures led to release of the contaminated allografts. Cultures of the corneas collected immediately before implantation yielded C. perfringens, indicating that the tissue donor likely had disseminated C. perfringens disease. ... The findings from this investigation underscore the serious infectious complications that can occur from transplanted allografts containing clostridia. ... Neither FDA nor EBAA provide guidance specifically for detecting or inactivating clostridial spores on corneal allograft tissues. Cultures of corneal tissue are not performed routinely by eye banks before a corneal transplant procedure. Eye banks may elect to perform presurgical (e.g., corneal-scleral rim) cultures, and positive culture reports should be reported to the receiving surgeon or recipient eye bank. Cultures may be performed either before or at the time of surgery (4). However, presurgical cultures might not reliably predict endophthalmitis complicating corneal transplantation (10)."
9/1/2003	Tendon	Streptococcus pyogenes	1	Aseptically processed	[13]	"Although allograft infections are rare, they highlight the need for improved tissue evaluation and processing standards. … TP-A processed the allografts using aseptic technique and an antimicrobial solution, but no sterilization procedure (e.g., gamma

						irradiation) was used." GAS was found in all tissue cultures pre-processing but after aseptic processing cultures were negative and therefore distributed - discussed the need to "...validate methods used to obtain culture specimens after antimicrobial treatment or sterilization. …However, when systemic infection is not detected before tissue recovery, donor eligibility should be reconsidered if cultures of multiple allograft tissues from the same donor yield the same organism. Multiple positive cultures for the same organism, even those not specified as highly virulent by AATB, might indicate systemic disease and should be considered in the comprehensive evaluation of the donor. …If tissue is contaminated with GAS or other pathogenic, highly virulent organisms, standard protocols for sterilization should be employed by tissue processors when possible, or the tissue should be discarded."
4/26/2013	Cornea	LCMV	0 cornea donors	Aseptically processed	[14,15]	"…[T]hree previous cornea recipients [when LCMV was transmitted via organs and investigated in cornea recipients of the same donors] also did not develop LCMV infections (1,2). Physicians and public health practitioners should be aware that organ donors with suspected central nervous system infection, and some with intracranial hemorrhage without evidence of infection, could be infected with LCMV, especially when rodent exposure has occurred."
5/25/2021	Bone allograft with bone marrow	Tuberculosis	19	Aseptic - bone marrow mixed with bone with minimal processing and distributed soon after recovery	[16–19]	"All prospective tissue and organ donors should be routinely assessed for risk factors and clinical findings of tuberculosis. When these are present, laboratory testing for Mycobacterium tuberculosis should be strongly considered."
7/11/2023	Bone allograft with bone marrow	Tuberculosis	27	Aseptic - bone marrow mixed with bone with minimal processing and	[20]	Additional interventions are necessary to address gaps in transplant tissue safety in the United States. Informed consent, including discussion of infectious disease risks and alternative treatment options, is needed before patients receive tissue allografts, particularly those containing live cells, which carry a higher risk for disease transmission. Health care facilities should

				distributed soon after recovery		also implement tissue-tracking protocols similar to those required for solid organs and blood products. Routine postimplant monitoring should be conducted on all tissue allograft recipients, because prompt and systematic reporting of adverse events enables rapid implementation of mitigation measures among other recipients. This outbreak serves as another reminder that TB has not been eliminated from the United States, where up to 13 million persons of all ages are living with untreated and often undiagnosed latent TB infection (LTBI).†† Diagnosing LTBI and TB disease is challenging because diagnostic tests have imperfect sensitivity. In addition, LTBI is asymptomatic, and nonspecific TB disease signs and symptoms overlap with many other disease processes. Because tissue allografts containing live cells are stored frozen and have expiration dates months or even years after manufacture, ample time exists for both culture-based testing and additional scrutiny of donor medical records. To reduce the risk for M. tuberculosis transmission through tissue allografts, culture-based testing of donor tissues before product distribution should be strongly considered, and current recommendations stipulating rejection of donors with sepsis§§ should be followed. [§§ https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances]

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American Association of Tissue Banks®

July 7, 2025

Vinay Prasad, MD, MPH
Director
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Prasad,

The American Association of Tissue Banks (AATB) appreciates the opportunity to comment on the Food and Drug Administration (FDA) draft guidance document titled, "Recommendations to Reduce the Risk of Transmission of Disease Agents Associated with Sepsis by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)." AATB appreciates that the agency has taken the important step of reissuing this guidance in draft form rather than as a direct-to-final guidance document for immediate implementation, and we recognize that this document contains important revisions compared to the previous version from January. We are concerned, however, that this draft guidance document presents numerous challenges to the industry, described below, which we hope the FDA will work to address in collaboration with AATB.

AATB is a professional, non-profit, scientific, and educational organization. AATB is the only national tissue banking organization in the United States, and its membership totals more than 125 accredited tissue banks and over 7,000 individual members. These banks recover tissue from more than 70,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants performed annually in the US. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

We share and support FDA's mission to ensure the safety and availability of donated tissue, and we appreciate the FDA's recognition that collaboration with industry stakeholders is critical for the success of this effort.

In drafting this letter, AATB solicited feedback from dozens of technical, scientific, and medical subject matter experts from accredited tissue banks.

This letter describes our industry's broad concerns about the classification of sepsis as a relevant communicable disease agent or disease (RCDAD), which is more problematic today than when FDA first made the decision to consider sepsis as an RCDAD. In 2007, FDA issued Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (DE Guidance), which defined sepsis as an RCDAD; however, that definition did not seem to comport with the actual definition of an RCDAD, as this letter will explain. Our comments also address specific provisions of the draft guidance with recommendations, where applicable, for changes to strengthen the proposed guidance.

Concerns with the Classification of Sepsis as an RCDAD

AATB understands that the FDA chose to designate sepsis as an RCDAD in 2007 with the hope that it would help identify potential donors who may pose a risk of transmitting infectious diseases. However, it

has become clear that the use of a clinical diagnosis of sepsis as a surrogate for transmissible infectious disease is not scientifically appropriate, given the term's conventional use in clinical practice. Rather, for purposes of determining the eligibility of an individual to serve as a tissue donor, the concern is whether a patient either suspected of having sepsis or with a sepsis diagnosis has an underlying infection that poses a risk to the recipient of tissue from that individual.

One of our chief concerns is that the use of a sepsis diagnosis as a bright line indicator may unintentionally lead to formulaic decision-making – rather than a careful evaluation process to determine whether donors have a systemic infection (regardless of whether the donor has a dysregulated immune response to the infection). By relying on sepsis as a surrogate for potentially infectious or transmissible disease agents, such as *Mycobacterium tuberculosis*, this draft guidance – if finalized – may also contribute to the unnecessary exclusion of otherwise eligible donors.

Sepsis Does Not Meet FDA's Conditions for RCDADs

RCDADs must fulfill 3 characteristics to meet the definition provided by the FDA, those being (1) Risk of transmission, (2) Severity of effect, and (3) Availability of appropriate screening measures or tests. While AATB agrees with FDA's definition of sepsis, described in the draft guidance as "a clinical syndrome defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Ref. 1)" as defined by Singer, et al.,[1] AATB does not agree that sepsis meets the criteria for definition as an RCDAD for the following reasons (2025 draft guidance quoted, any bold/italics were added for emphasis):

> **A. Risk of Transmission**
> "There is a risk of transmission by HCT/Ps of **any infectious agent that could cause sepsis.** Various bacterial (including mycobacterial), fungal, and viral agents have been shown to be transmissible via use of HCT/Ps (Refs. 7-13), and these agents have sufficient incidence and/or prevalence to affect the potential HCT/P donor population. **Bacterial infection potentially resulting in sepsis with associated morbidity and mortality** is a recognized risk from transfused blood and blood components (Refs. 14-15) and from transplanted organs (Refs. 16-18)."
>
> **AATB Comment:** The *infection (disease agent)* is what conveys the risk associated with tissue product, not the potential result of sepsis (it is not possible to *transmit* a dysregulated host *response* to infection).
>
> For example, consider someone who dies of COVID-19-associated sepsis. That donor would not transmit sepsis by tissue transplant to a recipient. This concept is applicable to the vast majority of non-infectious causes meeting the Systemic Inflammatory Response Syndrome (SIRS) criteria (which in a typical hospital setting would often be termed/coded as "sepsis"), such as myocardial infarction, embolisms, strokes, trauma, etc. In essence, using sepsis as the RCDAD is misleading and would erroneously skew donor evaluation to excluding safe donors.
>
> **B. Severity of Effect**
> **"**Sepsis could be fatal or life-threatening*, result* in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure."
>
> **AATB Comment:** Sepsis is **not** a transmissible disease. Therefore, sepsis itself does <u>*not result*</u> in risk to the recipient.
>
> Sepsis is a "host specific/personal" chemical and physiologic dysregulated immune response and cannot be transmitted. One can acquire influenza and die from a dysregulated response to it (i.e., sepsis), and yet another person can acquire the same influenza and have minor symptoms and

recover (i.e., appropriate, regulated immune response). **The dysregulated response itself is not transmissible.**

C. Availability of Appropriate Screening and/or Testing Measures
"Appropriate screening measures have been developed for detection of sepsis (see below). Sepsis is a clinical diagnosis and, as such, there are no specific testing measures to detect sepsis that serve to prevent the transmission of a pathogen that causes sepsis. However, testing for pathogens that may cause sepsis is available."

AATB Comment: Clinically, screening for sepsis is a pre-mortem prognostic tool utilized to predict mortality and enables implementation of rapid preventative measures, *not a diagnostic tool for detecting infection.*

Sepsis screening tools specifically measure physiologic responses (temperature, heart rate, respiratory rate, blood pressure, white cell counts, lactic acid level, oxygen level) in the setting of a possible or suspected infection and is separate from the evaluation for an infection, which may not be a systemic infection.

In the cited Singer reference ("Sepsis-3"),[1] the consensus task force states that, "What *differentiates sepsis from infection* is an aberrant or dysregulated host response and the presence of organ dysfunction." Furthermore, "The sepsis illness concept is predicated on infection as its *trigger*, acknowledging the current challenges in the microbiological identification of infection. It was not, however, within the task force brief to examine *definitions of infection*."

Changing Practices in US Healthcare and Clinical Considerations
Sepsis has been defined by FDA as an RCDAD since the August 2007 DE guidance. At the time of the publication of the DE guidance,[2] sepsis was clinically understood according to the 2001 International Sepsis Definitions Conference criteria.[3] Those 2001 criteria were intended to provide a consistent definition of sepsis based on evolved scientific understanding, and provided diagnostic criteria that included the following explicit acknowledgements that:

1) the diagnostic criteria were not specific to sepsis;
2) infection is often not microbiologically confirmed; and
3) there is a need for good bedside clinical judgment in the application of the diagnostic criteria.

Understanding of sepsis physiology, management, and epidemiology has further evolved since that time, and the most recent 2016 sepsis criteria[1] were aimed at updating definitions, aiming to decrease reliance on inflammation and SIRS criteria that have poor sensitivity and specificity, provide greater consistency for epidemiologic studies and clinical trials, and facilitate improved management of patients with sepsis. Because there are multiple consensus definitions of sepsis (e.g., CMS, Sepsis-3), current literature indicates there is still no universally accepted standard for the application of the term sepsis in clinical practice, particularly with respect to presence of infection.[4–6] The current FDA guidance on sepsis now appears to equate this clinical syndrome with a systemic infection.

The fact that there are different definitions of sepsis in use today is a challenge that is exacerbated by two important changes that have occurred in US healthcare since sepsis was first considered an RCDAD in 2007, both of which contribute to an increase in the likelihood that clinical impressions or working diagnoses are labeled as sepsis. These changes include a number of payment reforms instituted by the Centers for Medicare and Medicaid Services (CMS), as well as the increase in adoption of electronic medical records.

Many professional societies, clinical groups, and even the Office of the Inspector General (OIG) have noted that hospital coding and billing practices around sepsis can vary as a function of billing incentives

and are rife with accuracy concerns (OIG is expected to release a report in 2026 determining if hospitals in the US are relying on a broader definition of sepsis that is favored by CDC and CMS).[7,8]

Clinicians often include sepsis in a differential diagnosis to ensure timely and potentially life-saving treatment. However, subsequent diagnostic evaluation frequently reveals that the physiological manifestations initially attributed to sepsis may instead be due to non-infectious etiologies. As such, the presence of a sepsis diagnosis alone may not reliably indicate an underlying transmissible infectious disease.

In light of these concerns, AATB found it helpful to revisit *why* providers diagnose sepsis in the clinical setting. Providers identify those patients who are at a higher risk of mortality or excess morbidity from a dysregulated host response to an infection and diagnose them with sepsis or possible sepsis to facilitate the initiation of rapid and early treatment for that dysregulated physiology while they search for any *possible* infection. Mortality in patients with a dysregulated host response to a suspected infection, in the presence of organ dysfunction, is increased by approximately 10%, and higher if shock develops.[1] Sepsis is a prognostic tool, and though it is used clinically as a diagnosis code, *it is not, nor was it ever intended to be a* ***screening or diagnostic tool*** *for infection*. The infection suspicion component of current sepsis definitions (both CMS and Sepsis-3)[1,9] is separated from the organ dysfunction and host dysregulation criteria and what is an infection or suspicion of infection has never been defined by any of the consensus groups.

This confusion is perpetuated by the frequent use of the copy-paste (also known as copy-forward) function in electronic medical records (EMRs), which often results in redundant or outdated diagnoses being inappropriately carried forward. The phenomenon is well-documented and is referred to in the literature as "note bloat," "diagnostic drift," and "copy-paste propagation error."[10] Redundant Diagnosis Propagation occurs when a diagnosis from prior notes may persist even if they are resolved or inaccurate. An example of this is demonstrated when a resolved sepsis diagnosis may appear repeatedly in notes long after clinical resolution, or after the physician has determined that infection was not present. Both the failure to document resolution and failure to document ruling-out of a differential diagnosis decrease the value and reliability of sepsis documentation and necessitate further thorough evaluation of the donor by medical directors using the methods described above.[10]

Proposal
AATB respectfully requests that the FDA:

- Adopts a more specific and scientifically accurate framework—by designating "systemic infection" as an RCDAD (instead of sepsis) —to better reflect the intended risk assessment for transmissible disease. This refinement would enhance the clarity and utility of donor screening criteria while maintaining the FDA's commitment to public health and safety.
- Develops guidance aimed at reducing the risk of infectious disease transmission that prioritizes objective evidence of systemic infection over clinical suspicion of sepsis. We believe that systemic infection more appropriately meets the definition of an RCDAD, as it presents a clearer and more direct risk of transmission of an infectious agent.

Additional Discussion and Considerations for RCDAD Classification
In relation to the comments above, AATB submits the following comments regarding the FDA's inclusion of sepsis as an RCDAD in the context of donor eligibility determination for HCT/Ps.

1. Clinical Nature of Sepsis and Diagnostic Limitations
As noted above, sepsis, as defined by the Sepsis-3 consensus, is not a discrete communicable disease, but a clinical syndrome characterized by a dysregulated host response to a suspected infection. Critically, this definition does not require laboratory confirmation of a pathogen. Rather, the diagnosis is often based

solely on clinical suspicion, with the primary goal of initiating prompt treatment to reduce the risk of morbidity and mortality.

Given the relatively low risk associated with early empiric antibiotic therapy, clinicians frequently adopt a low threshold for including sepsis in the differential diagnosis—particularly in vulnerable populations such as the elderly and those with multiple comorbidities. As a result, sepsis is often diagnosed presumptively and may remain listed in the patient's medical record throughout the hospital stay, even when subsequent objective laboratory data fail to confirm the presence of a systemic infection, and even when other causes for the observed organ dysfunction have been identified.

This diagnostic pattern underscores the provisional and often non-specific nature of sepsis as a clinical label, further supporting the position that it does not meet the criteria for classification as an RCDAD.

2. Evidence from Sepsis-3 Validation and Clinical Practice
The Sepsis-3 validation study defined suspected infection using two criteria: the ordering of a bodily fluid culture and the subsequent initiation of antibiotic therapy. These actions are based on clinical judgment and typically occur early in the patient's hospital course—within 48 hours of admission in 86% of cases, and most frequently in the emergency department (44%).[4] Notably, a causative pathogen was identified in only a minority of cases. Of all encounters involving suspected infection, 76% were based on clinical presumption, while only 5% were confirmed cases of bacteremia.[4]

Noting that sepsis is estimated to be present in 30% to 50% of hospitalizations culminating in death, Rhee and colleagues performed a study to evaluate the prevalence, underlying causes, and preventability of sepsis-associated mortality in acute care hospitals. In this study, the immediate causes of death that were listed as sepsis were the result of solid cancer, chronic heart disease, hematologic cancer, dementia, and chronic lung disease, and that the majority of those sepsis deaths were deemed unpreventable.[11]

These findings highlight the diagnostic uncertainty surrounding sepsis and reinforce that it is not a reliable indicator of tissue-transmissible infection.

3. Additional Benefits of a Risk-Based, Evidence-Driven Approach
There are additional reasons why focusing on systemic infection instead of sepsis may be a more appropriate approach to take with respect to this guidance document. In particular, "systemic infection" broadens the scope under which donors who may pose a risk of disease transmission can be identified, thereby enhancing public safety. For example, in some previously confirmed cases of tissue-associated infectious disease transmission, a clinical diagnosis of sepsis was not present. These include a fatal case involving *Clostridium* species attributed to postmortem bacterial overgrowth,[12] and a case of *Group A Streptococcus* transmission from a donor with an unrecognized streptococcal bacteremia at the time of death.[13]

These examples demonstrate that reliance on a clinical impression of sepsis is insufficient to identify all scenarios in which infectious disease transmission may occur. Systemic infection may also be present in potential donors who do not develop sepsis (due to no dysregulated host response or organ dysfunction) and may indeed be determined eligible because the infection may be isolated/localized and does not convey transmissible risk to the recipient. Furthermore, localized within particular tissues may *not* cause sepsis in a potential donor, but are still of high risk for tissue transmissibility, such as tuberculous lesions isolated to a specific bone, bacterial cellulitis of the skin which is being recovered, or a purulent joint or tendon infection in tissue being evaluated for eligibility for transplant.

A medical director must be able to evaluate a donor's risk of any transmissible infection with the full clinical context of the available relevant medical records, which may not have been fully available to the treating physician at the time of the clinical encounter (e.g., final laboratory results, biopsy reports, autopsy, detailed medical and social history, etc.). Though certainly not sufficient alone for determining

the presence or absence of transmissible infection, in the risk-based approach favored by AATB, the clinical culture results would play a significant role in the eligibility determination of potential donors. In other words, a risk-based approach—grounded in professional medical evaluation of donor risk factors along with objective clinical, laboratory, and microbiological data—offers a more scientifically sound and effective framework for assessing donor eligibility and safeguarding public health.

Let us then evaluate the utility of cultures in the scope of both culture-negative and culture-positive sepsis. The draft sepsis guidance states that: "The causative agents in sepsis include bacterial, mycobacterial, fungal and viral pathogens. In a study that included data from 2013-2015 involving 225 adult patients and 75 pediatric patients from 4 acute care hospitals in New York, the *pathogens causing sepsis were not identified in over 31% of adult patients*. However, when a pathogen was identified, the most commonly identified organisms were bacteria, and 97% of the adult patients had at least one comorbidity (Ref. 5)." This cited a CDC and New York Department of Health collaborative study, which, while useful for hospital sepsis prevention and intervention initiatives, is both very small and biased towards severe sepsis and septic shock, with cases being identified by these *discharge diagnosis* codes rather than objective definitions. It may also have included skin contaminants as positive cultures, citing no particular method of evaluation of each culture, despite coagulase-negative staphylococcus spp. etc. being noted, and no effort to identify if the sepsis was identified by the physician as being caused by the particular organism or how many bottles or sets were positive. The *culture-positive* rate (not only blood, but any type of positive culture) in this study is presumably approximately 69%, taking these flaws into account.

Other more robust studies state that culture-positive sepsis (any culture, not solely blood cultures) is cited as closer to 40%, with approximately *60% of sepsis diagnoses having no causative organism found. The consensus "Sepis-3"[1] paper cites* 30-40%. Afzal et al (a meta-analysis involving 23,973 patients) found 40% culture-positive sepsis.[14]

Regardless of whether the true number of sepsis cases without a causative organism identified is closer to 31% or 60%, we need to evaluate the possible explanations for *why* causative organisms were *not* identified:

- One concerning possibility is the potential for *false-negative blood (or other) cultures*.
- The other possibility is that there was a *non-infectious* cause of dysregulated host response and organ dysfunction after appropriate infectious workup was done.

AATB submits that the finding of 31-60% of sepsis cases with underlying infectious causes *not found* does not automatically equate to those 31-60% having an unidentified systemic or transmissible infection by HCT/Ps. Rather, we believe a large proportion of these clinical sepsis syndromes diagnosed with initial "suspicion of infection" were appropriately worked up and can ultimately be determined to have non-infectious causes. Treating clinicians *must* diagnose and treat sepsis early (and without instantaneous full patient histories and final results available), which results in many initial sepsis diagnoses being ultimately determined false once information is gathered and finalized, if reviewed in full. This is expected, as sepsis screening is meant to be *sensitive* for dysregulated host response and organ dysfunction (to capture those at increased risk of dying), but not specific for infection. After a patient is deceased, there is often less utility in a treating physician retrospectively analyzing the final results that become available to determine the validity of the diagnosis. Therefore, it is uncommon, in our experience, to document that sepsis was ruled out or resolved unless the patient survives the initially presumed sepsis and dies later while hospitalized for another cause.

For the reasons stated, AATB believes the tissue establishment medical director generally has more data available to assess the potential for a systemic infection in donors at the time of death. AATB does not assume that ALL cases of culture-negative sepsis are without risk of transmissible infection. False-negative blood cultures *do* occur and here we outline the reasons for which medical directors must carefully evaluate blood (and other) cultures which are available to them for reliability:

1. **Inappropriate Number and Timing of Cultures**:
    - could miss transient bacteremia from local infections that are less likely to disseminate
    - collection after prior antibiotic therapy (timing can be assessed in EMR)

2. **Inadequate Volume:**
    - usually rejected or flagged by laboratory

3. **Slow-growing/fastidious, non-culturable, or difficult to grow organisms:**
    - less prominent now for bacteria with more advanced, automated blood cultures, but does still occur
    - these organisms are best assessed by evaluation of donor risk factors, donor exposures, and evaluating other objective clinical data (e.g., radiology, etc.)

False negative blood culture results should not be ignored but are indeed *rare*. In a large study of 12,406 blood cultures "Gram staining of blood cultures identified as negative in an automated system revealed typical slow-growing pathogens in **0.13%.**"[15]

Surprisingly, sepsis in patients for which any culture is identified as positive does not render higher mortality than those with culture-negative sepsis;[16] "Culture positivity or negativity was not associated with mortality of sepsis or septic shock patients. Furthermore, culture-positive septic patients had similar ICU length of stay, mechanical ventilation requirements, and renal replacement requirements as those culture-negative patients."[17]

One can postulate that this lack of increased risk of death may be due to the inherent definition of sepsis as a dysregulated host response with organ dysfunction, which is the actual risk to the patient, rather than the infection itself.

AATB therefore suggests it is important to consider the following question: What within current sepsis definitions *is* transmissible by tissue? It is certainly not organ dysfunction or a dysregulated host response. Underlying agents may or may not be transmissible by HCT/Ps**. Infections transmissible by HCT/Ps are those that are systemic/disseminated AND are present in the particular tissue being recovered**. A clinical condition's underlying agent may sometimes be transmissible to another individual, but evidence does not support that agent being rendered more or less infectious or transmissible when sepsis is present (examples: simple UTI, sinus infection) because it does not equate to the agent being present systemically or in the donated tissues. AATB submits that the safest approach to prevent infection transmission involves careful donor evaluation for risk of underlying agents potentially being present in the actual HCT/Ps being evaluated for eligibility.

Additional Proposals

Our strong recommendations for moving forward in developing the safest donor eligibility requirements are outlined below:

- **Modify the sepsis RCDAD determination:** First and foremost, we agree with FDA that a diagnosis of sepsis in a potential donor should be considered during eligibility determination. We believe that sepsis is a condition of concern and instead of being considered an RCDAD, it should be carefully evaluated given its *potential* association with an infectious agent.

- **Designate systemic infection as an RCDAD:** Evaluating a potential donor for sepsis does not accurately identify or stratify the risks for **systemic infection**, which would more clearly meet the three RCDAD requirements and be more directly representative of a transmissible agent.

- **Continue to evaluate and identify individual agents with *unique* clinical and epidemiological risk factors as RCDADs:** These agents may or may not cause sepsis in a potential donor, but are still relevant communicable disease agents when risk factors are identified for transmissible infection by HCT/Ps in the manner in which they typically clinically present. Of note, AATB has developed strict guidelines (often exceeding those put forth by the recent draft FDA TB guidance) for TB donor risk evaluation[18,19] and eligibility determination. We submit that such RCDAD modification would more adequately reduce the risk of transmissible disease agents than relying on an RCDAD of sepsis.

- **Move towards evaluating risk of systemic infection with addition of guardrails**: Evaluate and stratify *quality* of clinical data points (including reason for hospitalization, if hospitalized, length and level of stay, appropriate lab and culture results, imaging, etc.) and require adequate high-quality clinical data points in order to consider a donor at risk of systemic infection to be eligible. This would provide additional guardrails against judging a donor eligible when there are inadequate data available to safely do so.

In the event that the donor eligibility determination fails to exclude a donor with an infection, processing is an integral layer of safety within tissue transplantation, and processing methods should not be excluded from consideration when assessing donors. The risk of infectious disease transmission in tissue transplantation arises from the presence of viable microorganisms within donor tissues that are not fully eliminated through processing that eliminates or kills microorganisms.

This risk is most effectively mitigated through validated sterilization techniques, such as irradiation and comprehensive chemical sterilization protocols. In contrast, tissues that are minimally processed, particularly those decontaminated solely through selective methods like antibiotic incubation, carry a comparatively higher risk of transmitting infectious agents.

Processing methods must be selected based on their ability to preserve the structural integrity, biocompatibility, and intended function of the final tissue product. However, the presence of a systemic infection in the donor significantly increases the likelihood that viable microorganisms may have disseminated into the microcirculation and become embedded in tissues at or near the time of death. This scenario represents the biggest challenge for tissue banks with respect to preventing infectious disease transmission.

Accordingly, donor eligibility assessments should prioritize the identification of donors at risk for systemic infection or intravascular tissue contamination at the time of death. It is the responsibility of the tissue bank medical director to review all relevant medical records and apply professional medical judgment to evaluate the potential for infectious disease transmission, considering the intended processing methods.

Medical directors may apply different thresholds for donor acceptance depending on whether the tissue will undergo terminal sterilization or be minimally processed. In some cases, it may be necessary to make two separate eligibility determinations for the same donor—one for tissues intended for sterilization and another for those that will remain minimally processed.

AATB is developing evidence-based guidelines for this evaluation in a working group and plans to finalize guidelines by the end of 2025. These guidelines are intended to support medical directors in stratifying risk based on the donor's medical history, circumstances of death, and the planned tissue processing approach. They also provide recommendations for donor acceptance in specific high-risk scenarios and outline the minimum objective clinical data required to ensure a thorough and scientifically sound risk assessment. Elements of these guidelines will include:

- **Evaluate donors for risk of infection with difficult to culture organisms**: Include assessment of donor immune and overall health status, and any risk-adding exposures.
- Additionally, evaluate and risk-stratify decision-making based on donated tissue type, processing, and sterility.
- **Methods for this evaluation are also to be included in the AATB upcoming guidelines as well as medical director education programs.**

Conclusion
AATB believes that using the word "sepsis" in medical records as a rule out for donation is not the best approach for safer donor selection as it is neither sensitive nor specific to detect the matter at hand, which is tissue-transmissible infections. The approach of using sepsis as an exclusion criterion will exclude many safe donors and does not necessarily prevent transmission of disease agents that often present without sepsis, including tuberculosis.

We instead propose a shift in regulatory focus from current syndromic labels to objective indicators of systemic or transmissible infection consistent with current scientific standards. AATB believes that a more appropriate approach is a comprehensive one that takes multiple factors into consideration, including donor characteristics and epidemiological exposures, adequacy of medical records and medical evaluation before donation, types of tissues recovered, and the processing methods used. We are in the process of completing such guidelines, which will be an integral part of AATB education sessions and will more effectively identify unsafe donors while preserving access to safe, life-enhancing tissue. We urge FDA to work with AATB to challenge outdated definitions and align HCT/P RCDAD regulatory policy with scientific evidence and practical clinical reality, which we appreciate is reflected in the current overall agency public health goals.

Thank you again for rescinding the previously issued final guidance document and for reissuing this guidance in draft form. A table follows on the next page with additional comments from AATB. We appreciate your review of our recommendations and stand ready to assist the FDA in any way that you deem appropriate.

Regards,

Marc Pearce, MBA
President and CEO
American Association of Tissue Banks

Table 1 – Additional AATB Comments

FDA Guidance Reference	AATB Comment/Suggestion
"Per the Centers for Disease Control and Prevention (CDC), people are at higher risk for sepsis who are younger than one year old, 65 years or older, have weakened immune systems, chronic medical conditions (e.g., diabetes, lung disease, cancer, kidney disease), recent severe illness or hospitalization, or who are sepsis survivors"	The AATB agrees that there is a higher risk of sepsis (*dysregulated immune response to infection*) in these populations identified. More importantly, and more relevant to our purposes, however, there is a higher risk of systemic infection and immunosuppression with many of these listed conditions, which should prompt medical directors to evaluate donors with underlying risks for systemic infections and opportunistic infections with a higher level of suspicion in their overall review and eligibility determination regardless of presence or absence of a diagnosis of sepsis.
"The determination of sepsis as an RCDAD is based on the **risk of transmission by HCT/Ps of any agent that could cause sepsis**, severity of effect, and availability of appropriate screening measures, as discussed" [and] "There is a risk of transmission by HCT/Ps of **any infectious agent that could cause sepsis**."	For a pathogen that "could" cause sepsis, the presence of the pathogen in the body does not necessarily convey an additional risk to the recipient by HCT/Ps because sepsis was triggered, and evidence does not support the presence of sepsis contributes to the risk of transmissibility of that pathogen. This is best illustrated by a fatal COVID-19 sepsis that does not transmit SARS CoV-2 by non-lung tissues.
"You **must** determine to be ineligible any potential donor who is identified as **having a risk factor for sepsis**."	We seek clarification and modification of this wording. Does the FDA intend for this wording to suggest that all donors with any risk factor for sepsis (examples are age of 65+, diabetes, children <1 yr, those with lung disease, kidney disease, etc., as per CDC (https://www.cdc.gov/sepsis/risk-factors/index.html), must be determined ineligible solely because they have a risk factor for sepsis? The issue in the document here is the "should" statement directly following it (see below), therefore AATB seeks to modify this statement to : "Persons with risk factors for systemic infections should be carefully evaluated for eligibility to donate tissues, taking into consideration adequacy of medical records and patient evaluation, the tissues being recovered and the tissue processing methods used."
"The following conditions **should** be considered a risk factor: Persons who, currently, are known to have a medical diagnosis of sepsis or suspicion of sepsis from their most recent healthcare facility stay or visit preceding HCT/P recovery that is **not documented as resolved**."	There is discrepancy in wording between "*documented as resolved*" in the risk factor section vs "that is not resolved" in the clinical evidence section. We interpret "that is not resolved" to be per Medical Director's complete donor evaluation, whereas documentation implies

FDA Guidance Reference	AATB Comment/Suggestion
"…in accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who exhibits clinical evidence of sepsis. Examples of clinical evidence of sepsis may include: 1. medical records of a potential donor from their current hospital stay or other healthcare facility stay preceding HCT/P recovery, that document sepsis, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS) due to infection, or septic shock, **that is not resolved**. (Refs. 1-6, 19-22); 147"	that the treating physician needed to have documented resolution. Clarification is requested. AATB strongly recommends the assessment of the degree and the resolution of sepsis or its relevancy to the tissue being procured be left to the evaluation of the medical director in accordance to the guidelines under development by the AATB Sepsis working group and its recommendations and guardrails.
"Examples of clinical evidence of sepsis may include: ….2. clinical evidence of **current systemic infection exhibited by a potential donor that is consistent with risk of systemic infection and whose immune system was weakened** and unable to respond to infection (i.e., immunocompromised or immunosuppressed, such as due to age, a medical condition, or medication), or who is a recent sepsis survivor."	"Current systemic infection…consistent with risk of systemic infection…" is not a clear example of clinical evidence of sepsis. To reduce ambiguity and increase safety, AATB seeks to modify the statement to: "Persons with evidence of a systemic infection at time of donation should be ineligible to donate." Donors with weakened immune systems (i.e., immunocompromised or immunosuppressed, such as due to age, a medical condition, or medication) should be carefully evaluated for risks for and evidence of opportunistic infections or atypical presentations of infection.
"In this scenario, when feasible and appropriate, you should communicate (and document your communication) with the patient's primary treating physician to obtain additional information regarding their **patient's potential for higher risk of sepsis.**"	AATB questions if this was meant to be changed to "their patient's potential for higher risk of systemic infection" in the most recent draft edit. The paragraph begins by describing clinical evidence of systemic infection, but then asks for communication with the primary treating physician about higher risk for sepsis, which is not the agent of concern for transmission to a recipient. More appropriately, a medical director may, in the circumstance of clinical evidence of systemic infection that is not proven by culture, desire to specifically obtain additional information regarding a potential for undiagnosed systemic infection. An example of such an inquiry might be consultation with the treating cardiologist for additional records, including recent echo results, when a donor has risk factors for a fastidious organism that may cause endocarditis and is immunocompromised with negative blood cultures. In this example, additional information from an inquiry of "Was your patient at higher risk for sepsis?" is less likely to yield useful information for eligibility determination, whereas additional information regarding whether a patient

FDA Guidance Reference	AATB Comment/Suggestion
	met the Duke Criteria for endocarditis could reduce donor-derived transmission.

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